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Review

The role of nuclear matrix protein HNRNPU in maintaining the architecture of 3D genome

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ABSTRACT

The complexity of higher eukaryote genomes is far from being explained by linear information. There is a need to understand roles of genome regulation at the organism level through defining a comprehensive profile of chromosomal organization. Chromosome conformation capture (3C)-based studies reveal that higher-order of chromatin include not only long-range chromatin loops, but also compartments and topologically associating domains as the basis of genome structure and functions. However, the molecular machinery how the genome is spatially organized is still inadequate. Exciting progress has been made with the development of today's technology, we find that heterogeneous nuclear ribonucleoprotein U, initially identified as a structural nuclear protein, plays important role in three-dimensional (3D) genome organization by high-throughput assays. The disruption of this protein not only results in compartment switching on of the genome, it also reduces of TAD boundary strengths at borders between two types of compartments, and regulates chromatin loop by decrease its intensities. In addition, HNRNPU mainly binds to active chromatin. Most of HNRNPU peaks is consistent with CTCF or RAD21.It also plays an irreplaceable role in the processes of mitosis. This review aims to discuss the role of HNRNPU in maintaining the 3D chromatin architecture, as well as the recent development and human diseases involved in this nuclear matrix (NM)-associated protein.

Contents

1. Introduction

The eukaryotic genome functions as a complex, folded, three-dimensional (3D) environment, responsible for genome stability, transcriptional signaling, and cell proliferation and function [1–5]. Its structure determines function of RNA, protein, or entire DNA genome. The higher-order chromatin structure is formed and maintained with architectural proteins, such as the CCCTC-binding factor (CTCF) and cohesion [6]. CTCF is a universally expressed zinc finger protein, functions in transcriptional activation, repression, replication, recombination, and splicing [7], and is required for the recruitment of cohesin to chromatin [8]. Cohesin as a large ring-

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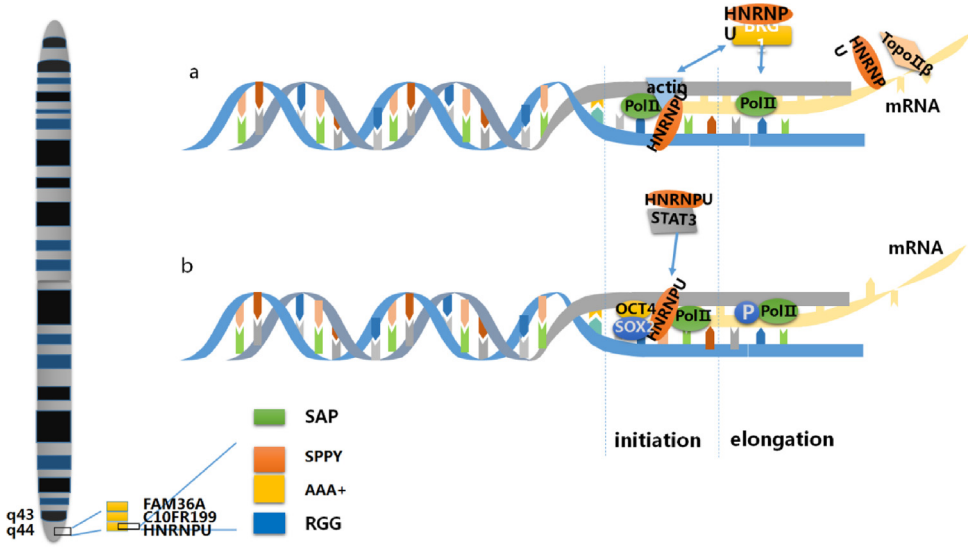

Fig. 1. HNRNPU located in chromatin1 q44 region, this region contains three genes, FAM36 A, C1ORF199, and HNRNPU. HNRNPU contains five regions. (a)HNRNPU and BRG1 are localize in the nucleus of mES cells and their interaction is required for global Pol II regulated transcription. Furthermore, both SAF-A and BRG1 have been reported to interact with actin and DNA topoisomerase IIβ. Actin and HNRNPU form a complex that plays a regulatory role in the initiation of transcription [87]. The RGG domain of HNRNPU could association with both topo IIβ and the endogenous RNA [46,88]. (b) SAF-A could interacts with the C-terminal region of endogenous RNA polymerase II and SAF-A exist in complexes with transcription factors sex determining region Y-box 2 (Sox2), Octamer-binding protein 4 (Oct4) and STAT3 in ES cells. Then HNRNPU can recruit unphosphorylated RNA pol II to start Oct4 transcription. Further it continues to interact with the phosphorylated RNA pol II to process the transcription elongation of nascent mRNA [43].

shaped molecule can bind to DNA strands to regulate the sister chromatid cohesion for proper chromosome segregation [9]. Other proteins, e.g. zinc finger143 [10], transcription activator Brahma-related Gene 1(BRG1) [11], and Runt-related transcription factor 1 [12], are also found to play roles in the regulation of chromatin interactions. In the inner and peripheral nuclear matrix, one of the nuclear matrix associated proteins, the heterogeneous nuclear ribonucleoprotein U (HNRNPU), is known as scaffold attachment factor A (SAF-A), as an abundant component of HNRNP particles.

HNRNPU links specific DNA elements, binds to scaffold/matrix attachment region, and is involved in the composition of higher order chromatin structure [13]. Such multifunctional protein plays a vital role in the recruitment of *XIST* RNA in inactive X chromosome [14] and a specific role in 3D genome organization by decompacting chromatin, rather than other HNRNP members [15]. In the present article, we overview the characteristics of HNRNPU and its role in maintaining the 3D genome structure, as well as recent developments in this regard.

2. HNRNPU biology

HNRNPU is also named SAFA, HNRPU, SAF-A, pp120, EIEE54, GRIP120, hnRNP U; HNRNPU-AS1. HNRNPU protein is encoded by the HNRNPU gene located on chromosome 1q44 [16], two differentially polyadenylated mRNAs. HNRNPU belongs to the subfamily of heterogeneous nuclear ribonucleoproteins (hnRNPs), to bind RNA, form complexes with heterogeneous nuclear RNA, and contribute to the processing of heterogeneous nuclear RNA to mRNA [17]. In addition, those proteins also contribute to pre-mRNA packaging and processing in the nucleus as well as mRNA metabolism and transport. hnRNPs are present in the nucleus, while some may shuttle between the nucleus and the cytoplasm [18].

HNRNPU is an abundant nucleoplasmic phosphoprotein about 120 kDa, as the largest one of hnRNP proteins [19]. Of 160 amino acids in the N-terminal of the HNRNPU protein, the most are acidic, e.g. aspartic and glutamic acid, while 112 amino acids in the C-terminal, are particularly rich with glycine responsible for RNA binding. Such glycine-rich RNA binding domain (U-gly) can be further localized to 26 amino acids to form a group of RGG repeats domain of RNA-binding [20], and possess an ATP-binding AAA^+ domain to promote the assembly. HNRNPU has five conserved domains, of which SAF/Acinus/PIAS (SAP) motif possess DNA binding activity, the adjacent region is an inherently unstructured peptide loop, SPla and RYanodine receptor (SPRY) of unknown function, AAA^+ domain, and RGG RNA-binding domain [15] (Fig. 1).

In the nucleus, HNRNPU is mainly involved in transcription and splicing process [21], as described in Fig. 1. The transcription can up-regulate HNRNPU, while the deficiency of HNRNPU has little effect on nascent RNA or steady-state RNA levels [15]. HNRNPU plays a central role in maintaining normal interphase structure of chromatin and is considered as a key target for apoptotic protease [22]. At the early stage of apoptosis, the signal of HNRNPU appears regular network in the nuclei, and then the HNRNPU connection with chromatin disappears completely [23] (Fig. 2). HNRNPU binds DNA to RNA of the same sequence as an attachment factor linking specific DNA elements, binding to scaffold/matrix attachment region [13]. HNRNPU is a bifunctional protein, of which one is pre-mRNA packaging and the other is involved in higher order organization of chromatin. About half of the HNRNPU is structurally fixed in the nucleus by a tight and stable pattern binding to the nuclear scaffold [24], while the other half is equally distributed between a soluble population and a DNase I extractable population [13]. The purified HNRNPU protein has two isoforms on basis of primary structure, of which both can bind RNA and link to single-stranded and double-stranded DNA [25].

3. HNRNPU regulates chromatin compartments

The whole genome is divided into A and B spatial compartments, associated with either open and expression-active chromatin or closed and expression-inactive chromatin, respectively [26]. The “A” compartment is often gene-rich, possesses high GC-contents, and is located in the center of nucleus, while the “B” compartment is relatively gene-poor, compacted and located around the periphery of nuclear. Both are consisted mostly of lamina-associating domains and contain late replication origins. Using

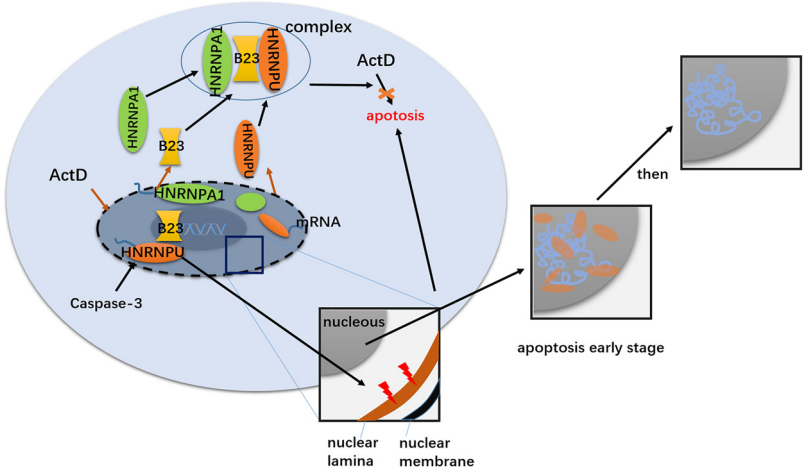

Fig. 2. Actinomycin D (ActD) can imitate the process of transcriptional arrest-induced nucleolar segregation. B23 is a nucleolar protein involved in many cellular activities, which located in the nucleus, whereas HNRNPU and hnRNPA1 are mainly in the nucleoplasm. ActD can promote the interaction of these three in the cytoplasm to become B23–HNRNPU–HNRNPA1 complex which can resist the apoptosis induced by nuclear stress, and such complex are regulated by HNRNPU-bound mRNAs for example Bcl-xL mRNA. Besides this kind of apoptosis is different from the apoptosis mediated by mitochondria. During apoptosis process, HNRNPU is cleaved by caspase-3 at a noncanonical cleavage site. Moreover, the protein proteolysis of HNRNPU seems to promote the destruction of the peripheral nuclear lamina. At the early stage of apoptosis, the signal of HNRNPU appears regular network in the nuclei, and then the HNRNPU connection with chromatin disappears completely.

super-resolution microscope [27] and single cell Hi-C [28], compartments A and B are found as relatively stable physical structures in individual cells. The *in situ* Hi-C assay is used to produce high-resolution interaction maps and analyze the impact of HNRNPU on chromatin interactions [29]. In the HNRNPU depleted cells, the inter-compartment interactions between A and B appreciably increased, while the interactions of compartments between A and A or B and B significantly reduced. The interaction in the intra-compartment appreciably increased in the A compartments, while decreased in the B compartments. It indicates that HNRNPU plays an important role in remodels of long-range interactions at the compartment level, e.g. between chromatin-chromatin and chromatin-lamina. The switching of A-to-B compartments can increase the interaction of chromatin-lamina and reduce gene expression, while the switching of B-to-A compartment shows oppositely [30].

4. Regulatory roles of HNRNPU

4.1. TAD

A topologically associating domain (TAD) is a self-interacting genomic domain, of which the three-dimensional chromosome structure is present in mammalian, plants, fungi, or bacteria [31]. A number of proteins are involved in the formation of TAD, including the CCCTC-binding factor and the complex cohesin [32]. Insulated neighborhoods, DNA loops, formed by CTCF/cohesin-bound regions, are proposed to functionally underlie TADs [33]. TAD boundaries were divided into three parts within compartment A or B, or between A and B. Most boundaries of TAD are located at the borders of A and B compartments and down-regulated when HNRNPU is depleted [30]. HNRNPU regulates TAD boundaries and TAD interactions in a compartment-specific and dependent way at the edges of compartments observed by Hi-C contact map.

4.2. CTCF and RAD21

CCCTC-binding factor (CTCF) is considered to be the most important participant in linking genome organization with gene expression and interacts with specific DNA sequences and many other architectural proteins, e.g cohesin [34]. Thus, CTCF can regulate DNA looping, serve as a transcriptional repressor, activator, and insulator at self-interacting domain boundaries and anchor the chromatin to the nuclear lamina [35]. CTCF and RAD21 are components of cohesin complex, and located in nucleus with HNRNPU. HNRNPU mainly connects with active chromatin, during which 80% of HNRNPU consistently binds with CTCF or RAD21, respectively. Furthermore, co-immunoprecipitation evidences that those three components are interlinked [30], although it remains unclear whether the correlation is direct or indirect.

4.3. Chromatin loops

Chromatin loops is the first level of nuclear organization involved in chromosomal folding and brought DNA regions on linear chromosome into close contacts together in three-dimensional space [36]. In higher eukaryotes, distal enhancer elements are important in the regulation of gene expression [37]. The enhancer function model is proposed that the enhancer and its target promoter are in direct contact with each other in space [38]. Recent studies demonstrate that each enhancer affects a variety of promoters, between which there is a complex network relationship [39]. The gene expression and enhancer-promoter interaction appear in the regulation of higher-order 3D chromatin characterized by multi-scale interaction networks [40]. Long-range chromatin loops play an important role in connecting enhancers and promoters, as well as insulating chromatin domains [30].

HNRNPU as scaffold attachment factor A is one of the main scaffold attachment region DNA-binding proteins in human cells, and related to the nuclear architecture via fastening chromatin loops to a proteinaceous nuclear skeleton [41]. Because of the complex regional structure, HNRNPU can be combined with DNA, including satellite DNA, and scaffold/matrix attachment DNA sequences, and RNA. HNRNPU is involved in higher order chromatin structure on basis of its high affinity for several homologous and heterologous scaffold/matrix attachment components. This is also a prerequisite for the formation of chromatin loops in the in vivo system [13]. Purified HNRNPU and scaffold/matrix attachment component can reconstruct looped structures [42] (Fig. 3). The overall advantages of chromatin loops decreased in HNRNPU-depleted cells. HNRNPU regulates chromatin loops and interphases chromosome structure via oligomerization. Lack of HNRNPU can cause

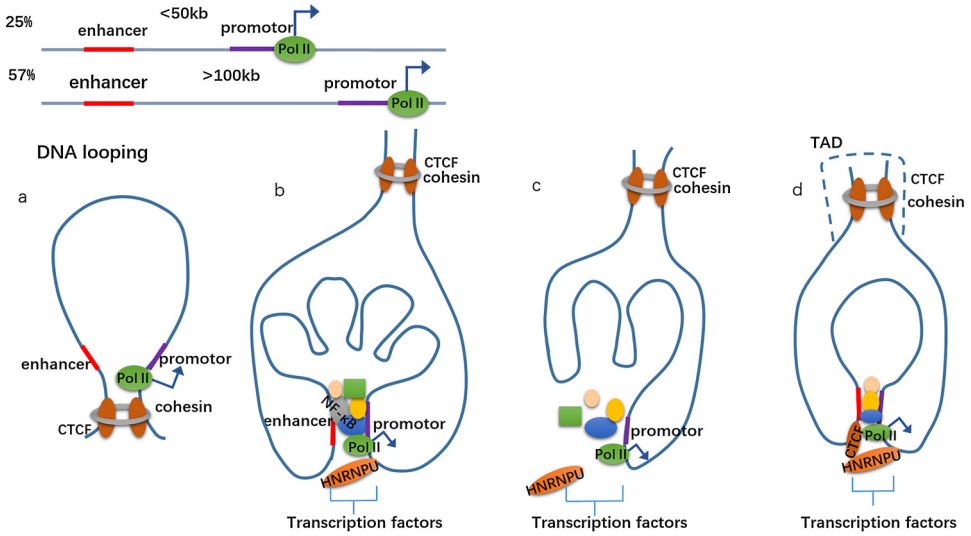

Fig. 3. About 25% of enhancer–promoter pairs are within a 50-kb range, and about 57% range 100 kb or larger genomic distance. (a) In some cases, enhancers and promoters interact before binding to signal-dependent transcription factors. In general, (b) a distal enhancer has at least one active promoter, or possibly two or more active promoters to form miniloops favored by many dispersed enhancer elements. Interestingly, (c) there are some active genes that do not react to any distal enhancer which is unnecessary to direct enhancer-promoter contact. CTCF maintains topologically associated domains with cohesion, and subdomains regulate the formation of chromatin loop, which are supported by two CTCF binding sites. (d) Interaction between CTCF binding sites and adjacent enhancers promotes functional interaction between enhancers and promoters.

chromosomal instability in this phase [15]. HNRNPU interacts with chromatin-associated RNAs through its RGG domain, which relies on HNRNPU's AAA^+ ATPase region. Such specific region can mediate cycles of HNRNPU oligomerization with chromatin-associated RNAs by binding RNA with ATP binding and hydrolyzing ATP. HNRNPU oligomerizes via ATP binding in vivo, to assembly and disassembly regulate the large-scale chromatin structure in a transcription-dependent manner [15]. HNRNPU creates transcriptionally active chromatin loops by binding RNA and DNA [43], and interacts with gene promotors by the regulation of many factors.

4.4. Transcriptions

Transcriptional state determines three-dimensional chromatin organization of most eukaryotes [44], where HNRNPU plays an important role in the process of transcription especially the processes of initiation and elongation. The endogenous HNRNPU may regulate the function of transcription factor, Octamer-binding protein 4 expression (Oct4), via binding the Octamer-binding protein 4 proximal promoter in embryonic stem cells [45]. HNRNPU could interact with the C-terminal domain of endogenous RNA polymerase II which is characterized with un-phosphorylation of C-terminal domain during initiation. The complex between HNRNPU and RNA pol II with a phosphorylated C-terminal domain can be formed in transcription elongation. Furthermore, HNRNPU also forms the complex with other transcription factors, including sex determining region Y-box 2 (Sox2), Oct4, or STAT3, which can be down-regulated due to lack of HNRNPU (Fig. 1). In addition, HNRNPU interacts with endogenous BRG1 protein in stem cells on the existence of mRNA. Such interaction between both is continuous during cell differentiation and regulates global transcription of RNA pol II, even though the exact mechanism is not clear [46]. During the transcriptional elongation in vivo, BRG1 helps RNA pol II to overcome nucleosomal barrier by binding with acetylated histone [47]. HNRNPU needs to interact with BRG1 for RNA polymerase II regulated transcription. BRG1 as a chromatin-modifying factor could regulate DNase I sensitivity, H3ac, and H3K4me2 methylation at both sites and contribute to chromatin loop formation, nucleosome remodeling, and transcriptional activation of the alpha globin locus [48]. HNRNPU can control a network of genes, e.g. Oct4, Nanog, and Klf2, at the phase of transcription initiation and elongation [49].

5. HNRNPU roles in mitosis

HNRNPU is located in spindles, spindle midzone and cytoplasmic bridge during mitosis, while mainly exists in the nucleus at interphase. HNRNPU begins to be relocated on spindle microtubules, when cells enter the phase of mitosis, while on the mitotic spindle at metaphase. HNRNPU is also found in the spindle midzone and eventually gathered in the cytoplasmic bridge at anaphase and telophase, respectively [50] (Fig. 4). HNRNPU has three types of positioning on the metaphase plates: outside the chromosomes, on the surface of the chromosome arms, probably scaffold/matrix attachment region DNA elements, and in the centromere region where it specifically binds to the satellite DNA [23].

HNRNPU contributes to the attachment of spindle microtubules to kinetochores and spindle organization [50] to form the complex which interacts with chromosome peripheral nucleolin and the spindle regulators, e.g. Aurora kinase A (Aurora-A) and Targeting protein for Xklp2 (TPX2) to further form a larger complex. During the formation of the complex, HNRNPU recruits Aurora-A to the mitotic spindle microtubules in Aurora-A- or TPX2-dependent patterns. It was evidenced by the fact that HNRNPU was largely disassociated from spindle microtubules due to lack of TPX2 or Aurora-A. HNRNPU is colocalized with TPX2 and Aurora-A as spindle regulators in spindle poles and microtubules to control the mitotic process, chromosome alignment, and spindle assembly [50] (Fig. 5). The centromere protein-W as an inner kinetochore plate formed a functional kinetochore complex with centromere protein-T. HNRNPU can increase the stabilities of centromere protein-W and T via binding the C-terminus domain. The presence of total RNA or mRNA in eukaryotic cells is the precondition of centromere protein-W-HNRNPU complex formation, of which both are mainly allocated in the nuclear matrix region and at the microtubule-kinetochore interface during interphase and mitosis, and can interact during mitosis [51]. HNRNPU can be phosphorylated or dephosphorylated by polo-like kinase 1 and protein phosphatase 2 A for mitosis [52]. The mutation of HNRNPU gene on serine 59 could produce a number of abnormal mitoses, contain-

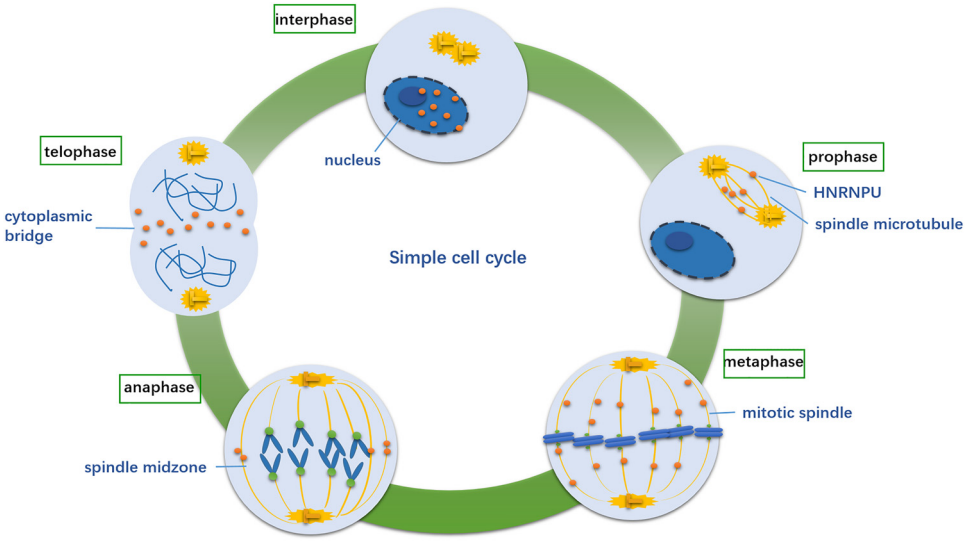

Fig. 4. In the cell cycle, HNRNPU present in different positions at different time. At interphase, HNRNPU was mainly existed in the nucleus. At prophase, HNRNPU begins to locate on spindle microtubules. And then it is located in the mitotic spindle. At anaphase and telophase, HNRNPU found in the spindle midzone and eventually gathered in the cytoplasmic bridge, respectively.

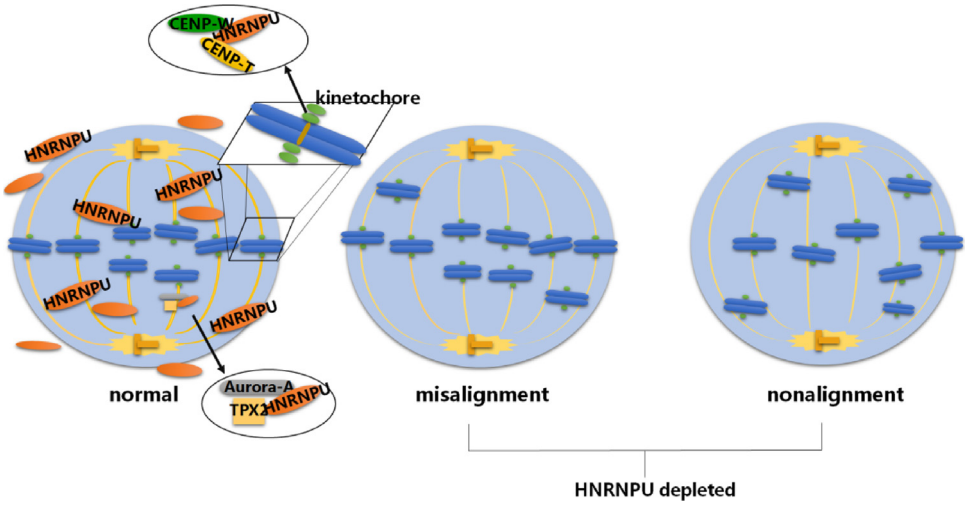

Fig. 5. Under normal circumstances, HNRNPU is present in spindles, spindle midzone and cytoplasmic bridge. In the prometaphase, the kinetochoresare distributed on the mitotic spindle. while, in HNRNPU depleted cells, the presence of kinetochores often outside the spindle. There are two kinds of chromosomal congression abnormalities in HNRNPU- depleted cells: misalignment and non-alignment. In the first defect phenotype, less than ten chromosomes are outside the spindle, while other chromosomes aligned at the spindle equator. In the another case, more than ten chromosomes are distributed outside the spindle. Furthermore, HNRNPU as a novel spindle regulator which could interact with other spindle regulators including Aurora-A and TPX2 during kinetochore–spindle microtubules attachment and mitotic spindle organization. In addition, centromere protein –W associate with HNRNPU also play critical role in the phase of kinetochore-microtubule attachment.

ing misaligned chromosomes, lagging chromosomes, polylobed nuclei, or delayed passage through mitosis [53]. Any abnormality of HNRNPU phosphorylation and dephosphorylation of can result in the pathogenesis during mitosis [54].

6. HNRNP-associated diseases

The family members of HNRNPs play the critical role in the enhance or splicing repression of RNA [55] and in the maintenance of cellar homeostasis in physiological and pathophysiological conditions, e.g. cancer or neurodegenerative diseases [56]. HNRNPU is normally expressed in the fetal brain, adult heart, kidney, liver, brain, and cerebellum [57], so humans *de novo* mutations or microdeletions of HNRNPU gene could lead to the development of brain disorders [58,59]. Preclinical studies demonstrated that 1q44 deletions of HNRNPU could induce the irregulation of embryonic brain development [60]. The 1q44 region contains FAM36 A, C1ORF199, and HNRNPU [16], of which the microdeletions could lead to the clinical features of intellectual disability, seizures, corpus callosum abnormalities, or microcephaly in patients [57,60,61]. It is still questioned which of FAM36 A, C1ORF199, and HNRNPU causes the corresponding clinical phenotypes and phenomes. The mutations of HNRNPU were found to represent early onset epilepsy and severe intellectual disability, evidenced by the finding that the non-sense variant, missense variant, intragenic deletion, and duplication of HNRNPU were correlated with main pathological changes [62]. In such findings were proved in seven patients with HNRNPU mutations, despite of the limited number of patients [63].

The mutation of HNRNPU is also proposed to contribute to the carcinogenesis and cancer development. For example, heparanase enhancer RNA promotes cancer development via driving chromatin looping and regulating the HNRNPU complex and binds

to HNRNPU through its RGG domain [73]. After then, HNRNPU protein indispensable for heparanase enhancer RNA facilitated heparanase transcription in cancer cells [64]. The long non-coding RNAs regulates cell cycle regulation, survival, cheomothrapy response, and various biological processes [65–68]. For example, SFTA1P, a pseudogene derived from long non-coding RNA could bind with HNRNPU, upregulating HNRNPU activity and increasing cell sensitivity to cisplatin. Moreover, HNRNPU can enhance the expression of growth arrest and DNA-damage-inducible protein GADD45 alpha by stabilizing mRNA [69]. GADD45 is involved in the repair of DNA damage and promotes apoptosis [70]. The SFTA1P-HNRNPU-GADD45 alpha pathway can increase the sensitivity of lung squamous cell carcinoma to chemotherapy. It should be seriously considered about the role of HNRNPU in disease, as therapeutic targets or diagnostic biomarkers. More studies need to define the HNRNPU specify of disease types, severities, durations, and responses to drugs, as characterized for clinical application [71–82].

7. Conclusion

HNRNPU is the member of hnRNP subfamily to bind RNA. The present article overviews the biological role of HNRNPU in the regulation of chromatin architectures, such as TADs, chromatin loops, and compartments. HNRNPU acts as a major regulator of 3D genome gathered with CTCF and RAD21. The abnormality of HNRNPU can condense the chromatin, switch the compartment, or decrease TAD boundary strengths and chromatin loop intensities. The major role of HNRNPU in higher-order chromatin organization depends on transcription and chromatin-associated RNAs through specific or non-specific binding. HNRNPU also interacts with long non-noncoding RNAs, including *Xist*, *Firre*, *LincGET*, *or Blen1* [83–86], regulate chromatin interactions in specific regions. The lncRNA-dependent role of HNRNPU in genome organization at specific sites need to be furthermore clarified. HNRNPU play a critical role in attaching of spindle microtubules to kinetochores and spindle organization in the process of mitosis as well as in the development of genome reorganizations in diseases. It is also possible that HNRNPU contribute to the formation of disease phenomes and cell injury. Although a large number of factors are involved in the regulation of HNRNPU, the specific regulatory mechanisms of HNRNPU-associated pathology remain unclear and will benefit the understanding of disease development.

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References

[1] M.J. Rowley, V.G. Corces, The three-dimensional genome: principles and roles of long-distance interactions, Curr. Opin. Cell Biol. 40 (2016) 8–14.
[2] T. Ma, L. Chen, M. Shi, J. Niu, X. Zhang, X. Yang, et al., Developing novel methods to image and visualize 3D genomes, Cell Biol. Toxicol. (2018).
[3] R. Li, Y. Liu, Y. Hou, J. Gan, P. Wu, C. Li, 3D genome and its disorganization in diseases, Cell Biol. Toxicol. (2018).
[4] P. Szalaj, D. Plewczynski, Three-dimensional organization and dynamics of the genome, Cell Biol. Toxicol. (2018).
[5] T. Terabayashi, K. Hanada, Genome instability syndromes caused by impaired DNA repair and aberrant DNA damage responses, Cell Biol. Toxicol. (2018).
[6] E. Gomez-Diaz, V.G. Corces, Architectural proteins: regulators of 3D genome organization in cell fate, Trends Cell Biol. 24 (2014) 703–711.
[7] C.T. Ong, V.G. Corces, CTCF: an architectural protein bridging genome topology and function, Nat. Rev. Genet. 15 (2014) 234–246.
[8] J.E. Phillips, V.G. Corces, CTCF: master weaver of the genome, Cell 137 (2009) 1194–1211.
[9] M. Merkenschlager, D.T. Odom, CTCF and cohesin: linking gene regulatory elements with their targets, Cell 152 (2013) 1285–1297.
[10] S.D. Bailey, X. Zhang, K. Desai, M. Aid, O. Corradin, R. Cowper-Sal Lari, et al., ZNF143 provides sequence specificity to secure chromatin interactions at gene promoters, Nat. Commun. 2 (2015) 6186.
[11] A.R. Barutcu, B.R. Lajoie, A.J. Fritz, R.P. McCord, J.A. Nickerson, A.J. van Wijnen, et al., SMARCA4 regulates gene expression and higher-order chromatin structure in proliferating mammary epithelial cells, Genome Res. 26 (2016) 1188–1201.
[12] A.R. Barutcu, D. Hong, B.R. Lajoie, R.P. McCord, A.J. van Wijnen, J.B. Lian, et al., RUNX1 contributes to higher-order chromatin organization and gene regulation in breast cancer cells, Biochim. Biophys. Acta 1859 (2016) 1389–1397.
[13] F. Gohring, F.O. Fackelmayer, The scaffold/matrix attachment region binding protein hnRNP-U (SAF-A) is directly bound to chromosomal DNA in vivo: a chemical cross-linking study, Biochemistry 36 (1997) 8276–8283.
[14] J. Wang, C.M. Syrett, M.C. Kramer, A. Basu, M.L. Atchison, M.C. Anguera, Unusual maintenance of X chromosome inactivation predisposes female lymphocytes for increased expression from the inactive X, Proc. Acad. Sci. U. S. A. 113 (2016) E2029–2038.
[15] R.S. Nozawa, L. Boteva, D.C. Soares, C. Naughton, A.R. Dun, A. Buckle, et al., SAF-A regulates interphase chromosome structure through oligomerization with chromatin-associated RNAs, Cell 169 (2017) 1214–1227, e18.
[16] B.C. Ballif, J.A. Rosenfeld, R. Traylor, A. Theisen, P.I. Bader, R.L. Ladda, et al., High-resolution array CGH defines critical regions and candidate genes for microcephaly, abnormalities of the corpus callosum, and seizure phenotypes in patients with microdeletions of 1q43q44, Hum. Genet. 131 (2012) 145–156.
[17] G. Dreyfuss, Structure and function of nuclear and cytoplasmic ribonucleoprotein particles, Annu. Rev. Cell Biol. 2 (1986) 459–498.
[18] G. Dreyfuss, M.J. Matunis, S. Pinol-Roma, C.G. Burd, hnRNP proteins and the biogenesis of mRNA, Annu Rev Biochem 62 (1993) 289–321.
[19] G. Dreyfuss, S.A. Adam, Y.D. Choi, Physical change in cytoplasmic messenger ribonucleoproteins in cells treated with inhibitors of mRNA transcription, Mol. Cell. Biol. 4 (1984) 415–423.
[20] M. Kiledjian, G. Dreyfuss, Primary structure and binding activity of the hnRNP U protein: binding RNA through RGG box, EMBO J. 11 (1992) 2655–2664.
[21] N.T. Vu, M.A. Park, J.C. Shultz, R.W. Goehe, L.A. Hoeferlin, M.D. Shultz, et al., hnRNP U enhances caspase-9 splicing and is modulated by AKT-dependent phosphorylation of hnRNP L, J. Biol. Chem. 288 (2013) 8575–8584.
[22] F. Gohring, B.L. Schwab, P. Nicotera, M. Leist, F.O. Fackelmayer, The novel SAR-binding domain of scaffold attachment factor a (SAF-A) is a target in apoptotic nuclear breakdown, EMBO J. 16 (1997) 7361–7371.
[23] A.S. Kukalev, I.B. Lobov, P. Percipalle, O.I. Podgornaya, SAF-A/hnRNP-U localization in interphase and metaphase, Cytogenet. Genome Res. 124 (2009) 288–297.
[24] K.A. Mattern, B.M. Humbel, A.O. Muijsers, L. de Jong, R. van Driel, hnRNP proteins and B23 are the major proteins of the internal nuclear matrix of HeLa S3 cells, J. Cell. Biochem. 62 (1996) 275–289.
[25] F.O. Fackelmayer, A. Richter, Purification of two isoforms of hnRNP-U and characterization of their nucleic acid binding activity, Biochemistry 33 (1994) 10416–10422.
[26] S. Nothjunge, T.G. Nuhrenberg, B.A. Gruning, S.A. Doppler, S. Preissl, M. Schwaderer, et al., DNA methylation signatures follow preformed chromatin compartments in cardiac myocytes, Nat. Commun. 8 (2017) 1667.
[27] S. Wang, J.H. Su, B.J. Beliveau, B. Bintu, J.R. Moffitt, C.T. Wu, et al., Spatial organization of chromatin domains and compartments in single chromosomes, Science 353 (2016) 598–602.
[28] T.J. Stevens, D. Lando, S. Basu, L.P. Atkinson, Y. Cao, S.F. Lee, et al., 3D structures of individual mammalian genomes studied by single-cell Hi-C, Nature 544 (2017) 59–64.
[29] S.S. Rao, M.H. Huntley, N.C. Durand, E.K. Stamenova, I.D. Bochkov, J.T. Robinson, et al., A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping, Cell 159 (2014) 1665–1680.
[30] H. Fan, P. Lv, X. Huo, J. Wu, Q. Wang, L. Cheng, et al., The nuclear matrix protein HNRNPU maintains 3D genome architecture globally in mouse hepatocytes, Genome Res. (2017).
[31] J.R. Dixon, S. Selvaraj, F. Yue, A. Kim, Y. Li, Y. Shen, et al., Topological domains in mammalian genomes identified by analysis of chromatin interactions, Nature 485 (2012) 376–380.
[32] A. Pombo, N. Dillon, Three-dimensional genome architecture: players and mechanisms, Nat. Rev. Mol. Cell Biol. 16 (2015) 245–257.
[33] X. Ji, D.B. Dadon, B.E. Powell, Z.P. Fan, D. Borges-Rivera, S. Shachar, et al., 3D chromosome regulatory landscape of human pluripotent cells, Cell Stem Cell 18 (2016) 262–275.
[34] E.D. Rubio, D.J. Reiss, P.L. Welcsh, C.M. Disteche, G.N. Filippova, N.S. Baliga, et al., CTCF physically links cohesin to chromatin, Proc. Acad. Sci. U. S. A. 105 (2008) 8309–8314.

[35] L. Guelen, L. Pagie, E. Brasset, W. Meuleman, M.B. Faza, W. Talhout, et al., Domain organization of human chromosomes revealed by mapping of nuclear lamina interactions, Nature 453 (2008) 948–951.
[36] F. Jin, Y. Li, J.R. Dixon, S. Selvaraj, Z. Ye, A.Y. Lee, et al., A high-resolution map of the three-dimensional chromatin interactome in human cells, Nature 503 (2013) 290–294.
[37] M. Bulger, M. Groudine, Functional and mechanistic diversity of distal transcription enhancers, Cell 144 (2011) 327–339.
[38] L.A. Pennacchio, W. Bickmore, A. Dean, M.A. Nobrega, G. Bejerano, Enhancers: five essential questions, Nat. Rev. Genet. 14 (2013) 288–295.
[39] G. Andrey, T. Montavon, B. Mascrez, F. Gonzalez, D. Noordermeer, M. Leleu, et al., A switch between topological domains underlies HoxD genes collinearity in mouse limbs, Science 340 (2013), 1234167.
[40] B. Doyle, G. Fudenberg, M. Imakaev, L.A. Mirny, Chromatin loops as allosteric modulators of enhancer-promoter interactions, PLoS Comput. Biol. 10 (2014), e1003867.
[41] M. Kipp, B.L. Schwab, M. Przybylski, P. Nicotera, F.O. Fackelmayer, Apoptotic cleavage of scaffold attachment factor A (SAF-A) by caspase-3 occurs at a noncanonical cleavage site, J. Biol. Chem. 275 (2000) 5031–5036.
[42] H. Romig, F.O. Fackelmayer, A. Renz, U. Ramsperger, A. Richter, Characterization of SAF-A, a novel nuclear DNA binding protein from HeLa cells with high affinity for nuclear matrix/scaffold attachment DNA elements, EMBO J. 11 (1992) 3431–3440.
[43] D. Vizlin-Hodzic, H. Johansson, J. Ryme, T. Simonsson, S. Simonsson, SAF-A has a role in transcriptional regulation of Oct4 in ES cells through promoter binding, Cell. Reprogram 13 (2011) 13–27.
[44] M.J. Rowley, M.H. Nichols, X. Lyu, M. Ando-Kuri, I.S.M. Rivera, K. Hermetz, et al., Evolutionarily conserved principles predict 3D chromatin organization, Mol. Cell 67 (2017) 837–852, e7.
[45] S. Tahmasebi, S.M. Jafarnejad, I.S. Tam, T. Gonatopoulos-Pournatzis, E. Matta-Camacho, Y. Tsukumo, et al., Control of embryonic stem cell self-renewal and differentiation via coordinated alternative splicing and translation of YY2, Proc. Acad. Sci. U. S. A. 113 (2016) 12360–12367.
[46] D. Vizlin-Hodzic, R. Runnberg, J. Ryme, S. Simonsson, T. Simonsson, SAF-A forms a complex with BRG1 and both components are required for RNA polymerase II mediated transcription, PLoS One 6 (2011), e28049.
[47] A. Subtil-Rodriguez, J.C. Reyes, BRG1 helps RNA polymerase II to overcome a nucleosomal barrier during elongation, in vivo, EMBO Rep. 11 (2010) 751–757.
[48] S.I. Kim, E.H. Bresnick, S.J. Bultman, BRG1 directly regulates nucleosome structure and chromatin looping of the alpha globin locus to activate transcription, Nucleic Acids Res. 37 (2009) 6019–6027.
[49] N. Ahmad, J.B. Lingrel, Kruppel-like factor 2 transcriptional regulation involves heterogeneous nuclear ribonucleoproteins and acetyltransferases, Biochemistry 44 (2005) 6276–6285.
[50] N. Ma, S. Matsunaga, A. Morimoto, G. Sakashita, T. Urano, S. Uchiyama, et al., The nuclear scaffold protein SAF-A is required for kinetochore-microtubule attachment and contributes to the targeting of Aurora-A to mitotic spindles, J. Cell Sci. 124 (2011) 394–404.
[51] Y. Chun, R. Kim, S. Lee, Centromere protein (CENP)-W interacts with heterogeneous nuclear ribonucleoprotein (hnRNP) U and May contribute to kinetochore-microtubule attachment in mitotic cells, PLoS One 11 (2016), e0149127.
[52] J.V. Olsen, M. Vermeulen, A. Santamaria, C. Kumar, M.L. Miller, L.J. Jensen, et al., Quantitative phosphoproteomics reveals widespread full phosphorylation site occupancy during mitosis, Sci. Signal. 3 (2010) ra3.
[53] Z. Shang, L. Yu, Y.F. Lin, S. Matsunaga, C.Y. Shen, B.P. Chen, DNA-PKcs activates the Chk2-Brca1 pathway during mitosis to ensure chromosomal stability, Oncogenesis 3 (2014) e85.
[54] P. Douglas, R. Ye, N. Morrice, S. Britton, L. Trinkle-Mulcahy, S.P. Lees-Miller, Phosphorylation of SAF-A/hnRNP-U serine 59 by polo-like kinase 1 Is required for mitosis, Mol. Cell. Biol. 35 (2015) 2699–2713.
[55] X.D. Fu, M. Ares Jr, Context-dependent control of alternative splicing by RNA-binding proteins, Nat. Rev. Genet. 15 (2014) 689–701.
[56] T. Geuens, D. Bouhy, V. Timmerman, The hnRNP family: insights into their role in health and disease, Hum. Genet. 135 (2016) 851–867.
[57] G. Thierry, C. Beneteau, O. Pichon, E. Flori, B. Isidor, F. Popelard, et al., Molecular characterization of 1q44 microdeletion in 11 patients reveals three candidate genes for intellectual disability and seizures, Am. J. Med. Genet. A 158A (2012) 1633–1640.
[58] K.C. Epi, Epilepsy Phenome/Genome P, A.S. Allen, S.F. Berkovic, P. Cossette, N. Delanty, et al., De novo mutations in epileptic encephalopathies, Nature 501 (2013) 217–221.
[59] R. Gupta, M. Agarwal, V.R. Boqqula, R.V. Phadke, S.R. Phadke, Hemiconvulsion-hemiplegia-epilepsy syndrome with 1q44 microdeletion: causal or chance association, Am. J. Med. Genet. A 164A (2014) 186–189.
[60] A. Caliebe, H.Y. Kroes, J.J. van der Smagt, J.I. Martin-Subero, H. Tonnies, R. van' t Slot, et al., Four patients with speech delay, seizures and variable corpus callosum thickness sharing a 0.440 Mb deletion in region 1q44 containing the HNRPU gene, Eur. J. Med. Genet. 53 (2010) 179–185.
[61] E. Boland, J. Clayton-Smith, V.G. Woo, S. McKee, F.D. Manson, L. Medne, et al., Mapping of deletion and translocation breakpoints in 1q44 implicates the serine/threonine kinase AKT3 in postnatal microcephaly and agenesis of the corpus callosum, Am. J. Hum. Genet. 81 (2007) 292–303.
[62] N.C. Bramswig, H.J. Ludecke, F.F. Hamdan, J. Altmuller, F. Beleggia, N.H. Elcioglu, et al., Heterozygous HNRNPU variants cause early onset epilepsy and severe intellectual disability, Hum. Genet. 136 (2017) 821–834.
[63] C. Depienne, C. Nava, B. Keren, S. Heide, A. Rastetter, S. Passemard, et al., Genetic and phenotypic dissection of 1q43q44 microdeletion syndrome and neurodevelopmental phenotypes associated with mutations in ZBTB18 and HNRNPU, Hum. Genet. 136 (2017) 463–479.
[64] W. Jiao, Y. Chen, H. Song, D. Li, H. Mei, F. Yang, et al., HPSE enhancer RNA promotes cancer progression through driving chromatin looping and regulating hnRNPU/p300/EGR1/HPSE axis, Oncogene (2018).
[65] K.C. Wang, H.Y. Chang, Molecular mechanisms of long noncoding RNAs, Mol. Cell 43 (2011) 904–914.
[66] T.R. Mercer, M.E. Dinger, J.S. Mattick, Long non-coding RNAs: insights into functions, Nat. Rev. Genet. 10 (2009) 155–159.
[67] L. Qu, J. Ding, C. Chen, Z.J. Wu, B. Liu, Y. Gao, et al., Exosome-transmitted lncARSR promotes sunitinib resistance in renal cancer by acting as a competing endogenous RNA, Cancer Cell 29 (2016) 653–668.
[68] W.J. Gong, J.Y. Yin, X.P. Li, C. Fang, D. Xiao, W. Zhang, et al., Association of well-characterized lung cancer lncRNA polymorphisms with lung cancer susceptibility and platinum-based chemotherapy response, Tumour Biol. 37 (2016) 8349–8358.
[69] M. Yugami, Y. Kabe, Y. Yamaguchi, T. Wada, H. Handa, hnRNP-U enhances the expression of specific genes by stabilizing mRNA, FEBS Lett. 581 (2007) 1–7.
[70] L.F. Zerbini, Y. Wang, A. Czibere, R.G. Correa, J.Y. Cho, K. Ijiri, et al., NF-kappa B-mediated repression of growth arrest- and DNA-damage-inducible proteins 45alpha and gamma is essential for cancer cell survival, Proc. Acad. Sci. U. S. A. 101 (2004) 13618–13623.
[71] S. Singh, A.K. Shrivastava, In silico characterization and transcriptomic analysis of nif family genes from Anabaena sp PCC7120, Cell Biol Toxicol 33 (2017) 467–482.
[72] X. Wang, Clinical trans-omics: an integration of clinical phenomes with molecular multiomics, Cell Biol. Toxicol. 34 (2018) 163–166.
[73] Y. Zeng, X. Chen, H. Gao, X. Wang, An artificial intelligent single cell is part of the cell dream world, Cell Biol. Toxicol. 34 (2018) 247–249.
[74] L. Shi, B. Zhu, M. Xu, X. Wang, Selection of AECOPD-specific immunomodulatory biomarkers by integrating genomics and proteomics with clinical informatics, Cell Biol. Toxicol. 34 (2018) 109–123.
[75] W. Wang, B. Zhu, X. Wang, Dynamic phenotypes: illustrating a single-cell odyssey, Cell Biol. Toxicol. 33 (2017) 423–427.
[76] D. Long, T. Yu, X. Chen, Y. Liao, X. Lin, RNAi targeting STMN alleviates the resistance to taxol and collectively contributes to down regulate the malignancy of NSCLC cells in vitro and in vivo, Cell Biol. Toxicol. 34 (2018) 7–21.
[77] Y. Kawamura, J. Takouda, K. Yoshimoto, K. Nakashima, New aspects of glioblastoma multiforme revealed by similarities between neural and glioblastoma stem cells, Cell Biol. Toxicol. (2018).
[78] M. Xu, X. Wang, Critical roles of mucin-1 in sensitivity of lung cancer cells to tumor necrosis factor-alpha and dexamethasone, Cell Biol. Toxicol. 33 (2017) 361–371.
[79] D. Wu, X. Wang, H. Sun, The role of mitochondria in cellular toxicity as a potential drug target, Cell Biol. Toxicol. 34 (2018) 87–91.
[80] W. Wang, D. Gao, X. Wang, Can single-cell RNA sequencing crack the mystery of cells? Cell Biol. Toxicol. 34 (2018) 1–6.
[81] L. Shi, N. Dong, D. Ji, X. Huang, Z. Ying, X. Wang, et al., Lipopolysaccharide-induced CCN1 production enhances interleukin-6 secretion in bronchial epithelial cells, Cell Biol. Toxicol. 34 (2018) 39–49.
[82] X. Liu, J. Wu, History, applications, and challenges of immune repertoire research, Cell Biol. Toxicol. (2018).
[83] C. Chu, Q.C. Zhang, S.T. da Rocha, R.A. Flynn, M. Bharadwaj, J.M. Calabrese, et al., Systematic discovery of Xist RNA binding proteins, Cell 161 (2015) 404–416.
[84] E. Hacisuleyman, L.A. Goff, C. Trapnell, A. Williams, J. Henao-Mejia, L. Sun, et al., Topological organization of multichromosomal regions by the long intergenic noncoding RNA firre, Nat. Struct. Mol. Biol. 21 (2014) 198–206.
[85] J. Wang, X. Li, L. Wang, J. Li, Y. Zhao, G. Bou, et al., A novel long intergenic noncoding RNA indispensable for the cleavage of mouse two-cell embryos, EMBO Rep. 17 (2016) 1452–1470.
[86] L. Mi, X.Y. Zhao, S. Li, G. Yang, J.D. Lin, Conserved function of the long noncoding RNA Blnc1 in brown adipocyte differentiation, Mol. Metab. 6 (2017) 101–110.
[87] A. Kukalev, Y. Nord, C. Palmberg, T. Bergman, P. Percipalle, Actin and hnRNP U cooperate for productive transcription by RNA polymerase II. Nat Struct Mol Biol 12 (2005) 238–244.
[88] S. Kawano, M. Miyaji, S. Ichiyasu, K.M. Tsutsui, K. Tsutsui, Regulation of DNA topoisomerase IIbeta through RNA-dependent association with heterogeneous nuclear ribonucleoprotein U (hnRNP U), J. Biol. Chem. 285 (2010) 26451–26460.